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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,680	04/16/2007	Jo Klaveness	PN0399	7410

36335 7590 11/24/2009

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EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
11/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,680	KLAVENESS ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/24/2009 has been entered.

Acknowledgement of Receipt

Applicant's Response, filed 9/24/2009, in reply to the Office Action mailed 6/24/2009, is acknowledged and has been entered. Claims 1 and 8 have been amended. Claims 2-7, 9, 10, 12 and 13 have been cancelled. Claims 1, 8 and 11 are pending and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but they are moot in view of new grounds for rejection, necessitated by claim amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of optical imaging of vulnerable atherosclerotic plaque of an animate subject involving administering an optical contrast agent with an affinity for an abnormally expressed biological target associated with vulnerable atherosclerotic plaques, wherein said biological target is selected from: MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with proteins, angiotensin II receptors and collagens. The contrast agent has the formula V-L-R, wherein V is one or more vector moieties having affinity for an abnormally expressed target in vulnerable atherosclerotic plaques, L is a linker moiety or a bond and R is one or more reporter moieties detectable in in vivo optical imaging. However, the claims are devoid of any structural elements that correlate to the function which is to be achieved with the claimed composition. For example, a vast number of potential “vector moieties having an affinity for an abnormally expressed target in vulnerable atherosclerotic plaques” may be found in the art to be capable of having the

claimed function. Applicant has identified in the instant specification a diverse variety of targets for which the vector may have affinity including MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with proteins, angiotensin II receptors and collagens, etc. (see paragraphs 0025-0044 of the instant specification). Such targets are widely varying in structure and would have an almost unlimited number of potential vectors which may have affinity thereto. The vectors themselves may be almost unlimited including various pepdide sequences, small molecules, antibodies, nucleic acid sequences, etc. It is clear that Applicant had possession of such a few specific formulations at the time of filing using specific and defined vectors as identified in paragraphs 0057-0067 and 0088-0095 and the Examples, but the specification as originally filed does not provide support that Applicant had possession of the invention as generically claimed by function alone in the instant claims. For example, to arrive at the claimed contrast agent, one would have to determine the type of vector having affinity to which out of an extremely large number of targets to conjugate to which out of an almost unlimited number of potential optical imaging moieties to be combined into a single agent, and further which out of an almost unlimited number of potential functional groups or chemical reactions would be necessary to derivatize and conjugate the moieties into a single agent having the claimed functional properties, in order to provide a contrast agent to practice the claimed method. One would have to select which portions of which molecules would be suitable to be conjugated to the others and on what positions of the molecules with various substituents. Applicant's limited disclosure of a particular compound which has

the claimed functional properties for use in the claimed method does not provide support that Applicant envisaged the invention as a whole which is broadly claimed solely by function. In the instant case, a definition by function alone does not appear to sufficiently describe the claimed invention because it is only an indication of what the agent does, rather than what it is. See MPEP 2163 and *Eli Lilly,* 119 F.3 at 1568, 43 USPQ2d at 1406.

Applicant argues on pages 5-6 of the Response that the Examiner has acknowledged elsewhere in the office action that suitable vectors were already known, that the person skilled in the art can be assumed to be already aware of suitable targeting molecules for the biological targets of claim 1, and that the specification need not provide a comprehensive list of such vectors, since they were already within the common general knowledge of the person skilled in the art.

This is not found to be persuasive. The prior art documents represent a small genus of a few specific peptides that target MMP-9. However, the claims are inclusive of any of an very large genus of peptides, oligonucleotides, fat-related compounds, drug-like compounds, etc. that may serve as a vector. While Applicant has provided a description of a few specific vectors (i.e. a single peptide sequence which binds MMP (paragraph 0088), a single hydrazine derivative which targets oxidation product of phospholipid (0095) and a single small molecule which acts as a vector for angiotensin (paragraph 0067). Such a limited disclosure of a single vector for each of the claimed receptors which are associated with atherosclerotic plaque (MMP 9, toll-like receptors, scavenger receptors, oxidized LDL, oxidation products of lipids and their adducts with

proteins, angiotensin II receptors and collagens) does not provide sufficient description to show that Applicant was in possession of the full scope of a contrast agent comprising an optical imaging moiety and any vectors (e.g. any small molecule, any peptide, any oligonucleotide, any antibody etc) which may target the claimed receptors. The claims appear to define the vector by function, only giving an indication of what it does, rather than what it is, and the claims are more broad than the enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims include the limitations "fat-related compounds" and traditional organic drug-like small molecules." The claims are unclear because the identity of compounds which are to be encompassed by the claims are not clearly set forth. For example, it is unclear to what degree a compound should be "related" to a fat, or "like" a drug to be within the scope of the claims. Accordingly, the metes and bounds of the claims are not clearly set forth and the scope of the invention cannot be distinctly ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness *et al.* (US 2003/0170173), as evidenced by Penate *et al.* (*Cancer Research*, 2001, 61, p. 3978-3985), in view of Ntziachristos *et al.* (US 6,615,063).

Klaveness discloses contrast agents and the use of these contrast agents for diagnosis of diseases in humans and animals based on mapping of metabolic activity. The contrast agents can be used to identify tissue or cells with metabolic activity or enzymatic activity deviating from the normal (abstract). Contrast agents can be for optical imaging, including those having fluorophores, etc. (paragraph 0009 and 0107-0109). The contrast agents are conjugated with various enzymes substrates including MMP. Klaveness teaches that substrates For Human Matrix Metalloproteinase include Collagens, Proteoglycans, Laminin, Fibronectin, Gelatins, Elastin, Perlacan, Entactin, Vitronectin, Tenascin, Nidogen, Dermatan sulphate, proTNF-.A-inverted., Vitronectin, Aggrecan, Transin, Decorin, Glycoproteins. MMP could also be used according to the invention as possible targets for vulnerable atherosclerotic plaques. Reliable methods

for targeting vulnerable atherosclerotic plaques are currently missing. Vulnerable plaques tend to rupture and induce thrombosis, which may lead to occlusion of the vessel and acute myocardial infarction. As a further aspect of the invention it is suggested to detect MMP activity as targets for distinguishing between stable and unstable vulnerable atherosclerotic plaques. Degradation of the fibrous cap in the atherosclerotic plaque by MMPs destabilises the plaque and increases its vulnerability. The activity of these MMPs, or the new epitopes exposed after metalloproteinases digestion, could be targets for contrast agents (paragraphs 0194-0197). See especially Example 25, drawn to a gelatinase-binding peptide for imaging atherosclerotic plaques, and contrast agents for imaging atherosclerotic plaques by MRI and scintigraphy. Gelatinase is a metalloproteinase that is expressed by unstable atherosclerotic plaques. The cyclic peptide Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys was identified as a gelatinase inhibitor and is synthesized by solid phase techniques. The peptide is conjugated to DTPA and complexed with gadolinium or ^{99m}Tc for use in MRI or scintigraphic imaging of atherosclerotic plaque. The contrast agents for detecting enzyme activity are characterized in that the contrast agent substrate changes pharmacodynamic properties and/or pharmacokinetic properties upon a chemical modification of the contrast agent substrate to a contrast agent product upon a specific enzymatic transformation (claim 4).

The Penate reference is included to show that the Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys peptide (CTT), is a gelatinase targeting peptide which inhibits MMP-2 and MMP-9 (see page 3978).

Klaveness does not specifically conjugate Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys to an optical imaging contrast agent. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute an optical imaging agent such as a fluorescent dye for the DTPA chelates in Example 25 of Klaveness, and therefore to use such a contrast agent for optical imaging of vulnerable atherosclerotic plaque. One would have been motivated to do so, and would have had a reasonable expectation of success in doing so because Klaveness teaches that a variety of contrast agent substrates may be used including MRI contrast agent, a radiopharmaceutical contrast agent, an ultrasound contrast agent, an optical imaging contrast agent or an x-ray contrast agent (claim 8). See also paragraphs 0009 and 0107-0190. Even though Klaveness does not specifically recite that Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys targets MMP-9, it is known in the art to inherently do so, as shown by Penate.

Klaveness does not specifically recite that an optical probe is a cyanine dye.

Ntziachristos discloses that with regard to reporter fluorochromes: hundreds of optical probes have been developed for microscopy and photodynamic therapy. Of these, fluorescent probes (i.e., excitation at shorter wavelength and emission at longer wavelength) are ideally suited for studying biological phenomena, as has been done extensively in fluorescence microscopy. If fluorescent probes are to be used in living systems, the choice is generally limited to the near infrared spectrum (600-1000 nm) to maximize tissue penetration by minimizing absorption by physiologically abundant absorbers such as hemoglobin (550 nm) or water (1200 nm). Ideally the

fluorochromes are designed to emit at 800+-50 nm. A variety of molecules have been described and/or are commercially available, including: **Cy5.5** (Amersham, Arlington Heights, Ill.); NIR-1 (Dojindo, Kumamoto, Japan); IRD382 (LI-COR, Lincoln, Nebr.); La Jolla Blue (Diatron, Miami, Fla.); **ICG** (Akorn, Lincolnshire, Ill.); and ICG derivatives (Serb Labs, Paris, France). NIRF probes for in vivo use ideally should have the following properties: (1) narrow emission bandwidths, (2) high fluorescence efficiency (quantum yield), (3) biocompatibility, and (4) spectrally separated absorption and excitation (column 8, lines 42+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ a cyanine dye as the fluorescent agent or optical probe in the gelatinase-binding peptide conjugates of Klaveness used for e.g. imaging atherosclerotic plaques, and contrast agents for imaging atherosclerotic plaques. While Klavness recites that fluorescent or optical imaging probes may be used, Klaveness does not specifically recite cyanine dyes. One of ordinary skill would have been motivated to select a cyanine dye as the optical probe because Ntziachristos teaches that cyanine dyes (Cy5.5, ICG etc., which inherently have the claimed absorption properties) are commercially available, and one would have had a reasonable expectation of using said probes because they are known to have desirable properties such as fluorescence efficiency, biocompatibility, etc.

Claims 1, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith *et al.* (US 2004/0053823) in view of Ntziachristos *et al.* (US 6,615,063).

Smith discloses isolated MMP-2, MMP-9 and MT1-MMP selective substrate polypeptides or functional peptidomimetics. The selective substrate polypeptides contain the following sequences: **MMP-9** selective substrate polypeptides contain SEQ ID NOS:28-35 (abstract). A diagnostic moiety can be linked to a selective substrate polypeptide of the invention in an inactive form. This type of diagnostic moiety would be targeted to a site of metalloproteinase activity where it would be activated. For example, a **fluorescent probe such as a near-infrared fluorescence(NIRF) imaging probe** can be in an inactive or quenched state until it reaches a desired site where it can be converted to an active or un-quenched state (paragraph 0079). A diagnostic moiety can also be, for example, a MRI contrast dye or a **fluorescent agent**. In one embodiment, the invention provides an isolated MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention described above where the diagnostic moiety is a quenched fluorophore, for example, a near-infrared fluorescence (NIRF) imaging probe. These biocompatible, optically quenched NIRF imaging probes can generate a strong NIRF signal after enzyme activation such as hydrolysis by a proteinase. A NIRF imaging probe can be linked to a MT1-MMP, MMP-2, or MMP-9 selective substrate polypeptide of the invention in order to specifically target the NIRF imaging probe to a site of activity of these MMPs such as a tumor or a site of inflammation. The NIRF moiety linked to a selective substrate polypeptide of the invention can be used to define and measure a site of MMP activity, for example, this conjugate can be used to image a tumor (paragraph 0088). See also claim 25, drawn to an MMP-9 selective substrate peptide sequence of SEQ ID 28-35 conjugated to a

fluorophore diagnostic agent. The methods of the invention also can be useful for preferentially directing a moiety to angiogenic vasculature that is not tumor vasculature or associated with neoplastic disease. Neovascularization also has been described within the intima of human atherosclerotic lesions and, further, angiogenic inhibitors such as endostatin can reduce the intimal neovascularization and plaque growth evident in apolipoprotein E-deficient mice. Thus, a method of the invention can be useful for **preferentially directing a therapeutic moiety or imaging agent to angiogenic sites in atherosclerotic plaques** (paragraph 0127).

Smith does not specifically recite that a fluorescent agent or NIRF probe is a cyanine dye.

Ntziachristos discloses that with regard to reporter fluorochromes: hundreds of optical probes have been developed for microscopy and photodynamic therapy. Of these, fluorescent probes (i.e., excitation at shorter wavelength and emission at longer wavelength) are ideally suited for studying biological phenomena, as has been done extensively in fluorescence microscopy. If fluorescent probes are to be used in living systems, the choice is generally limited to the near infrared spectrum (600-1000 nm) to maximize tissue penetration by minimizing absorption by physiologically abundant absorbers such as hemoglobin (550 nm) or water (1200 nm). Ideally the fluorochromes are designed to emit at 800+-50 nm. A variety of molecules have been described and/or are commercially available, including: **Cy5.5** (Amersham, Arlington Heights, Ill.); NIR-1 (Dojindo, Kumamoto, Japan); IRD382 (LI-COR, Lincoln, Nebr.); La Jolla Blue (Diatron, Miami, Fla.); **ICG** (Akorn, Lincolnshire, Ill.); and ICG derivatives

(Serb Labs, Paris, France). NIRF probes for in vivo use ideally should have the following properties: (1) narrow emission bandwidths, (2) high fluorescence efficiency (quantum yield), (3) biocompatibility, and (4) spectrally separated absorption and excitation (column 8, lines 42+).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ a cyanine dye as the fluorescent agent or NIRF probe in the peptide conjugates of Smith used for e.g. preferentially directing a therapeutic moiety or imaging agent to angiogenic sites in atherosclerotic plaques. While Smith recites that fluorescent probe such as a near-infrared fluorescence (NIRF) imaging probe may be used, Smith does not specifically recite cyanine dyes. One of ordinary skill would have been motivated to select a cyanine dye as the optical probe because Ntziachristos teaches that cyanine dyes (Cy5.5, ICG etc., which inherently have the claimed absorption properties) are commercially available, and one would have had a reasonable expectation of using said probes because they are known to have desirable properties such as fluorescence efficiency, biocompatibility, etc.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS